cigarette smoking."[858] The memo offers the following rationale for documenting the "penalties" of discontinuation:

> The literature on the subject cites body weight gains up to twenty pounds. Constipation has been cited as another sequelae (Ejrup, 1965), as well as blisters in the mouth. Chessick (1964) has warned against the "neurovegetative disequilibrium" that can result and Masoni (1963) contends that some may not be able to stabilize emotionally. There is anecdotal and lay observation of lowered efficiency and heightened irritability upon withdrawal. We know, too, that in periods of non-voluntary deprivation, as in concentration camps of World War II, the incentive value of the cigarette exceeds that of essential foodstuff.[859]

The actual text of the memo thus demonstrates clearly that Philip Morris has knowledge of significant withdrawal symptoms associated with smoking deprivation. The memo displays no skepticism about the existence of the cited withdrawal symptoms.

8. Philip Morris argues that reports of animal research conducted in its laboratories by Philip Morris researchers Victor DeNoble and Paul Mele do not conclude that nicotine is addictive.

The reports in question showed that Philip Morris had established that nicotine functions as a "positive reinforcer" in rats (causes them to seek repeated doses), and has other psychoactive effects characteristic of addictive substances. *See* Jurisdictional Analysis, 60 FR 41754–41758. These reports also showed that Philip Morris conducted research to find nicotine analogues (substitutes) that would have equal or greater reinforcing and psychoactive effects as nicotine. *Id.* These central nervous system effects were characterized by Philip Morris as "desirable properties" of nicotine that could be

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[858] Dunn WL (Philip Morris Inc.), *Stating the Risk Study Problem* (Jul. 29, 1969), at 3. *See* AR (Vol. 15 Ref. 189-6).

[859] *Id.*

"enhanced" as a result of nicotine analogue research.[860] Finally, these research reports showed that Philip Morris conducted research to find an "optimum" combination of nicotine and acetaldehyde (another component of smoke) that had "maximal reinforcing effects."[861]

FDA disagrees that it inappropriately relied on these studies. FDA did not cite these documents for the proposition that Philip Morris acknowledged that nicotine is addictive. FDA cited them, appropriately, as evidence that Philip Morris: (1) had conducted research demonstrating that nicotine is a positive reinforcer, one of the characteristic features of addictive substances; and (2) understood that the pharmacological effects of nicotine were essential to the market for tobacco products and intended to offer products that affect the central nervous system. *See* Jurisdictional Analysis, 60 FR 41750–41762.

9. Philip Morris states that, during his tenure at Philip Morris, Victor DeNoble repeatedly advised his colleagues that the fact that a substance has positive reinforcement effects does not mean that the substance is "addictive."

FDA agrees that animal self-administration does not alone demonstrate conclusively that a substance will be addictive in humans. As DeNoble stated in his testimony before Congress, however, "[t]he self-administration study is a classical hallmark to indicate that a solution or drug substance has . . . the potential to be a drug of

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[860] Charles JL (Philip Morris Inc.), *Nicotine Receptor Program–University of Rochester* (Mar. 18, 1980). *See* AR (Vol. 32 Ref. 532).

[861] DeNoble VJ (Philip Morris Inc.), *Project Number 1610 (Behavior Pharmacology) Objectives and Plans 1982-1983* (Jul. 20, 1982), at 2. *See* AR (Vol. 345 Ref. 5443).

abuse in humans."[862] As described earlier, a drug's abuse liability refers to its potential to cause drug dependence/addiction.

As described in section II.A.3.c., above, a complete screen for abuse liability also includes studies that demonstrate that the drug's reinforcing effects are caused by its actions in the central nervous system, that the drug has psychoactive effects, that the drug produces withdrawal and/or tolerance. Philip Morris research also demonstrated that nicotine has each of these properties.[863] These results distinguish nicotine from such nonaddictive substances as saccharin, which are not psychoactive.

As described in section II.C.2.a.ii., above, corporate executives were informed that Philip Morris' own research predicted that nicotine would be a drug of abuse in humans. A reasonable manufacturer with this information should have foreseen that nicotine was likely to be addictive in humans.

10. Tobacco industry comments challenge the reliability of a report submitted by William A. Farone, director of applied research at Philip Morris from 1976 to 1984, entitled "The Manipulation and Control of Nicotine and Tar in the Design and

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[862] *Regulation of Tobacco Products (Part 2): Hearings Before the Subcommittee on Health and the Environment of the Committee on Energy and Commerce. U.S. House of Representatives.* 103d Cong. 2d Sess. 18 (Apr. 28, 1994) (testimony of Victor J. DeNoble). *See* AR (Vol. 708 Ref. 2).

[863] *See, e.g.*, Dunn WL (Philip Morris Inc.), *Plans and Objectives–1980* (Jan. 7, 1980), in 141 Cong. Rec. H7668, H7669 (daily ed. Jul. 25, 1995). *See* AR (Vol. 14 Ref. 175a).

DeNoble VJ (Philip Morris, Inc.) *Nicotine Program–Behavioral Research Laboratory* (Apr. 24, 1980), at 2. *See* AR (Vol. 345 Ref. 5446).

Ryan FJ (Philip Morris Inc.), *Bird-1: A Study of the Quit-Smoking Campaign in Greenfield, Iowa, in Conjunction with Movie, Cold Turkey* (Mar. 1971). *See* AR (Vol. 21 Ref. 207).

DeNoble VJ, Mele PC (Philip Morris Inc.), *Development of behavioral tolerance following chronic nicotine administration* (unpublished manuscript). *See* AR (Vol. 346 Ref. 5464).

Manufacture of Cigarettes: A Scientific Perspective." In this report, Farone describes the beliefs of Philip Morris, and, in some cases the tobacco industry, concerning: the essential role of nicotine in tobacco use; research conducted by the industry on nicotine's pharmacological effects; and techniques used by the industry to reduce tar while maintaining an adequate level of nicotine. Farone bases his report on personal knowledge, as well as company documents and published literature. The tobacco industry argues generally that the information in Farone's report should not be relied upon because: (1) many of his statements about Philip Morris or the industry are not supported by documentary evidence; and (2) Farone left Philip Morris in 1984 and therefore does not have personal knowledge of the current operations of the company.

Other comments argue that Farone's report provides additional factual support for the conclusion that Philip Morris scientists and executives understand and intend that the primary role of nicotine in Philip Morris' products is to provide nicotine's pharmacological effects to consumers. These comments also argue that Victor DeNoble, former research scientist for Philip Morris, has publicly confirmed the accuracy of many of the statements made by Farone. Finally, these comments argue that the reliability of the information provided by Farone, is enhanced by its consistency with the sworn testimony of the former vice president for research and development for Brown & Williamson.

FDA disagrees with the tobacco industry comments that Farone's report is not reliable evidence relevant to establishing the intended use of cigarettes. Farone was a high-ranking manager within Philip Morris, whose responsibilities gave him first-hand knowledge of the information presented in the report. As director of applied research, Farone supervised five research divisions with a total of 150 employees, mostly

professionals. He reported directly to the vice president for research and development and regularly met with other senior management officials, including the CEO and president of Philip Morris, to discuss Philip Morris activities related to basic and applied research, product and process development, manufacturing, and results of test marketing of new products.[864] He was thus in a position to have personal knowledge of the views and activities of Philip Morris concerning the topics discussed in his report. Thus, the fact that he does not cite documentary evidence to support each statement in the report is irrelevant to the weight to which the report is entitled.[865]

The fact that Farone left Philip Morris in 1984 also provides no basis to consider his report irrelevant. As discussed above in section II.C.2.e., the extensive collection of tobacco company statements relied on by the agency reflects a consistent pattern of tobacco industry views spanning three decades. These statements provide evidence of the long-standing knowledge and beliefs of tobacco company officials that cigarettes are primarily used by consumers for the pharmacological effects of nicotine. Farone's statements about the knowledge, beliefs, and actions of the tobacco industry are entirely consistent with the body of industry statements relied on by the agency, adding to their credibility. Moreover, Farone's statements are consistent with the recent Philip Morris

[864] Declaration of Uydess IL (Feb. 29, 1996), at 23-24. *See* AR (Vol. 638 Ref. 1).

[865] FDA notes that Philip Morris has submitted two affidavits from current employees which purport to provide, based on the personal knowledge of the affiants, information about the measurement of nicotine levels in reconstituted tobacco. Neither of these affidavits cites any documentary support. Thus, Philip Morris appears to believe that FDA is entitled to rely on information based on personal knowledge. Philip Morris Inc., Comment (Apr. 19, 1996), at appendix 3. *See* AR (Vol. 700 Ref. 226).

document concerning Project Table,[866] demonstrating that the company's views have not changed since Farone left the company.

11. Tobacco industry comments also challenge specific statements made in Farone's report. FDA addresses those comments that challenge statements cited by the Agency.

The tobacco industry contests Farone's statement that it is widely believed within the tobacco industry that nicotine is the primary reason people smoke. The industry argues that the documents cited by Farone do not support this statement, and that industry evidence shows that consumers do not smoke cigarettes "nearly exclusively" or "solely" for the pharmacological effects of nicotine.[867]

FDA disagrees with these comments. As described above and in sections II.C.6.a.ii. and iii., below, there is ample support, including the documents cited by Farone, for the conclusion that tobacco industry officials believe that people use tobacco primarily to obtain the pharmacological effects of nicotine. Moreover, as discussed above, Farone's position and responsibilities within Philip Morris were such that the statements based on his personal knowledge may be considered reliable evidence. Finally, Farone's statement is corroborated by the existence of dozens of similar statements by Philip Morris officials in other documents cited in section II.C.2.a.i., above, and in the Jurisdictional Analysis. *See* 60 FR 41584–41620.

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[866] Philip Morris, Inc., Draft Report Regarding a Proposal for a "Safer" Cigarette, Code-named *Table*. *See* AR (Vol. 531 Ref. 122).

[867] Philip Morris Inc., Comment (Apr. 19, 1996), at 57. *See* AR (Vol. 700 Ref. 226).

II.C.6.

The tobacco industry comments present no contradictory statements or other evidence to demonstrate that tobacco industry officials do not believe that nicotine is the primary reason people smoke. Instead, the industry argues that there is evidence that, in fact, consumers do not smoke cigarettes "solely" or "nearly exclusively" for the pharmacological effects of nicotine. These comments misconstrue the nature of the evidence required to establish intended use. The statements of Farone and others are properly used by FDA to show that Philip Morris *knows* that consumers use cigarettes for the pharmacological effects of nicotine. This knowledge is relevant to establishing the company's intent to affect the structure and function of the body. See 21 CFR 201.128 and 801.4. In establishing intended use through a manufacturer's actual knowledge, it is not necessary for the Agency to show knowledge that consumers use tobacco nearly exclusively for its pharmacological effects. *Cf. Action on Smoking and Health v. Harris,* 655 F.2d 236, 240 (D.C. Cir. 1980) (FDA must establish nearly exclusive consumer use for pharmacological effects only where there is no other evidence of manufacturer's intent).

Moreover, as described in section II.B., above, the scientific evidence demonstrates that the pharmacological effects of nicotine are the primary motivation for tobacco use, and that other aspects of tobacco use, such as flavor, are secondary. Indeed, the data show that tobacco users enjoy the flavor of tobacco products because they have come to associate its flavor with obtaining the pharmacological effects of nicotine. Thus, contrary to Philip Morris' comment, even though not necessary to establish "intended use," the evidence shows that consumers do use tobacco products nearly exclusively for the pharmacological effects of nicotine.

ii. Comments on Specific RJR Statements and Research Projects. Like Philip Morris, RJR argues that FDA misused statements and research reports by RJR officials that the Agency relied upon as evidence that RJR officials believe that consumers use cigarettes to obtain the pharmacological effects of nicotine. FDA has reviewed the statements and research reports in context and concluded that, with one minor exception, the Agency correctly relied upon them.

1. RJR argues that the 1972 memorandum by Claude Teague, assistant director for research at RJR,[868] cited by FDA, does not provide evidence of the intended use of cigarettes because Teague was only presenting a "hypothesis" to stimulate discussion, and because the document does not reflect institutional intent. RJR focuses heavily on the fact that one of the quoted paragraphs and a few other phrases in the document begin with "if" or otherwise suggest uncertainty.

At the time the Jurisdictional Analysis was published, two paragraphs from the memorandum that had been published in the *New York Times*. The complete nine-page memorandum was subsequently submitted to the Agency in a comment and is discussed above in section II.C.2.b.i. The full document demonstrates that RJR's assistant vice president for research asserted as fact, not hypothesis, that nicotine's pharmacological effects are the primary reason people smoke and that cigarettes are nicotine delivery systems. Before the paragraph that begins "If nicotine is the *sine qua non* of tobacco products," Teague says:

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[868] Teague CE (R.J. Reynolds Tobacco Co.), *Research Planning Memorandum on the Nature of the Tobacco Business and the Crucial Role of Nicotine Therein* (Apr. 14, 1972), at 1-2. *See* AR (Vol. 531 Ref. 125).

> Nicotine is known to be a habit-forming alkaloid, hence the confirmed user of tobacco products is primarily seeking the physiological "satisfaction" derived from nicotine—and perhaps other compounds . . . . Thus a tobacco product is, in essence, a vehicle for delivery of nicotine, designed to deliver the nicotine in a generally acceptable and attractive form. Our industry is then based upon design, manufacture and sale of attractive dosage forms of nicotine. . . .[869]

The actual text of the document thus flatly contradicts RJR's claim that Teague was making "suppositions" about nicotine that were "very tentative."[870] He was, instead, stating as established fact that people smoke for the pharmacological effects of nicotine. The later statement, "If nicotine is the *sine qua non* of tobacco," is thus not an "hypothesis" but a rhetorical device to encapsulate the author's previously expressed position.

2. In the Jurisdictional Analysis, FDA relied upon the statements of RJR researchers in published papers that many of the most important effects of smoking cited by smokers as the reasons they smoke are the pharmacological effects of nicotine. RJR argues that none of the papers asserts that the pharmacological effects of nicotine are the most important reason for smoking, and that the papers also refer to the role of nonpharmacological effects in smoking behavior. RJR also contends that these papers do not show that consumers use tobacco nearly exclusively for its pharmacological effects.

FDA disagrees. A fair reading of these studies indicates that the authors view nicotine as playing a far more significant role in smoking motivation than other, nonpharmacological motives.

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[869] *Id.* at 1.

[870] R.J. Reynolds Tobacco Co., Comment (Jan 2, 1996), at 30. *See* AR (Vol. 519 Ref. 103).

For example, a paper published in 1991 refers to the fact that some smokers report that they smoke to increase their mental alertness, while others smoke to calm their moods; the paper attempts to prove that both sets of motives can be attributed to the effects of nicotine on different hemispheres of the brain.[871] The study demonstrated that smoking produced EEG effects in different hemispheres of the brain, depending on the depth of inhalation, leading the researchers to conclude that "light inhaling . . . smokers may smoke primarily for purposes of mental activation and performance enhancement" while "an important motive for deep inhaling smokers might be anxiety reduction."[872] Nonpharmacological motives for smoking are not mentioned at all. In studies where they are mentioned, RJR researchers never claim that nonpharmacological motives are more important to the smoker than nicotine.

RJR's contention that its published studies do not demonstrate "nearly exclusive consumer use" of cigarettes for pharmacological effects does not diminish their relevance to establishing intended use. These studies were designed by RJR to examine the effects of smoking on the human brain and on behavior, not to quantify consumer use. These studies are properly used by FDA to show that RJR knows that consumers use cigarettes for the pharmacological effects of nicotine. A manufacturer's actual knowledge is relevant to establishing the intended use of these products to affect the structure and function of the body. See 21 CFR 201.128 and 801.4. Moreover, when the evidence of tobacco manufacturer's statements, research, and actions demonstrates that their products are

[871] Pritchard WS (R.J. Reynolds Tobacco Co.), Electroencephalographic effects of cigarette smoking, *Psychopharmacology* 1991;104:485-490. *See* AR (Vol. 3 Ref. 23-2).

[872] *Id.* at 488.